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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/043,933	03/30/1998	JEAN-MARC BALLOUL	017753-094	7553

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EXAMINER	
FOLEY, SHANON A	
ART UNIT	**PAPER NUMBER**
1648	

DATE MAILED: 05/16/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 09/043,933	**Applicant(s)** BALLOUL ET AL.	
	Examiner Shanon Foley	**Art Unit** 1648	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 28 April 2005 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☐ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires *4* months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on *28 April 2005*. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☒ Applicant's reply has overcome the following rejection(s): 112, first and second paragraphs.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: *none*.
   Claim(s) objected to: *none*.
   Claim(s) rejected: *105,107,117,118,130,134,135,138 and 139*.
   Claim(s) withdrawn from consideration: *10-20,25-31 and 86*.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See the attached correspondence.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08 or PTO-1449) Paper No(s). _____
13. ☐ Other: _____.

Shanon Foley
Primary Examiner
Art Unit: 1648

Request for Reconsideration

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 105, 107, 130, 134 and 135 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lowy et al., Galloway, Crook et al. and Munger et al. as applied to claims 89 and 124-128 above, and further in view of Bubenik et al. (International Journal of Oncology also maintain for claims 117, 118, 138 and 139 in view of Galloway, Bubenik et al., Crook et al. and Munger et al. for reasons of record.

Applicant argues that Lowy et al. teach that presentation of early peptides on the surface of a VLP is required to achieve therapeutic efficacy. However, this is evidently not the case since Lowy et al. claim a vaccine composition comprising L1 and L2 proteins without the inclusion of early papillomavirus peptides, see claims 1-4 and 22.

Applicant also states that Lowy et al. fail to provide any data supporting effective protection against HPV-tumors with the chimeric VLPs. However, Lowy et al. teach prophylactic efficacy with a composition comprising L1 and L2, see page 2, lines 47-59. In any case, the instant claims are drawn to a method of treatment, not prevention.

Applicant also asserts that Lowy et al. do not provide any data regarding the therapeutic effect of the chimeric VLPs with E7 on their surface. However, the instant rejection is based on a combination of teachings, which include the teachings of Galloway. Therapeutic efficacy by

inclusion of the early proteins is expressly suggested by Lowy et al. on page 2, line 28 to page 3, line 2 and page 7, lines 13-27. In addition, Galloway review data in the prior art that clearly indicate that L1 and L2 proteins have prophylactic properties and that E6 and E7 proteins have therapeutic properties, see the paragraph bridging pages 190-191. Therefore, the therapeutic efficacy of the early papillomavirus proteins E6 and E7 was established in the prior art, as evidenced by the review of data presented in the literature by Galloway.

Applicant argues that Galloway does not teach or suggest a composition comprising L1, L2, E6, E7 and an immunostimulatory polypeptide.

Applicant's arguments have been fully considered, but are found unpersuasive. It is evident from the teachings of Lowy et al. and Galloway that L1 and L2 have prophylactic properties and that E6 and E7 have therapeutic properties. As applicant states in the paragraph bridging pages 14-16, a prima facie case of obviousness is established when the combination of teachings from the references or knowledge available to one skilled in the art suggests a motivation or supplies an incentive to combine the references. In the instant case, the E6 and E7 are known in the prior art to be therapeutic against papillomavirus infection and L1 and L2 are known to be protective against papillomavirus infection. Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to combine L1, L2, E6 and E7 into a single vaccine composition to treat and prevent papillomavirus infection. Further, one of ordinary skill would have had a reasonable expectation of success for treating and preventing papillomavirus infection with a composition comprising L1, L2, E6 and E7 because L1 and L2 are prophylactic and E6 and E7 are therapeutic. Neither Galloway nor Lowy et al. teach IL-2. This limitation is taught by Bubenik et al. with a motivation to combine IL-2 with the

composition of Lowy et al., Galloway, Munger et al. and Crook et al. with a reasonable expectation of success.

Applicant states that Bubenik et al. teach the separate administration of huge quantities of IL-2. Applicant argues that Bubenik et al. does not provide a reasonable expectation of success for direct administration of L1, L2, E6, E7 and IL-2.

Applicant's arguments have been fully considered, but are found unpersuasive. Applicant has previously identified the 20 separate administrations of IL-2 taught by Bubenik et al. It is agreed that 20 separate injections of IL-2 would not be practical for human administration and the ordinary artisan would be motivated to eliminate the multiple administrations through combination. The quantity of IL-2 administered to mice to achieve the adjuvanting effect observed by Bubenik et al. would be different from the amount required for humans. The quantity required for sufficient administration is not a required element of the claims and even if it were, specific concentrations do not support patentable subject matter unless the concentration is considered critical to the invention, see *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). One of ordinary skill in the art at the time the invention was made would have been motivated to combine the IL-2 of Bubenik et al. with the early and late protein composition of Lowy et al. and Galloway to augment the immune response to the papillomavirus polypeptides while eliminating the tumor suppressive effects of E6 and E7. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of combining IL-2 with the proteins of Galloway, Lowy et al., Munger et al. and Crook et al. because Bubenik et al. specifically teach augmenting the function of papillomavirus vaccines with IL-2, see "Adjuvant effect..." and the discussion section on page 479.

Claims 117, 118, 138 and 139 are rejected under 35 U.S.C. 103(a) as being unpatentable over Galloway, Crook et al., Munger et al. and Bubenik et al. for reasons of record.

Applicant argues that Galloway does not teach or suggest the instant composition or even disclose IL-2.

Applicant's arguments have been fully considered, but are found unpersuasive. Claims 117, 118, 138 and 139 are drawn to a method of treatment by administering specific nononcogenic variants of E6 and E7 with IL-2. Munger et al. and Crook et al. teach the nononcogenic variants of E7 and E6, respectively. Galloway teaches therapeutic vaccines against HPV comprising E6 and E7, see the abstract on page 187 as well as pages 190-191. Galloway does not teach or suggest IL-2. However, Bubenik et al. do. The instant rejection is based on a combination of teachings in the prior art (emphasis added).

Applicant summarizes the teachings of Bubenik et al. and concludes that there is no reasonable expectation of success for combining the references requiring numerous injections of IL-2.

Applicant's arguments have been fully considered, but are found unpersuasive. Applicant has previously identified the 20 separate administrations of IL-2 taught by Bubenik et al. It is agreed that 20 separate injections of IL-2 would not be practical for human administration and the ordinary artisan would be motivated to eliminate the multiple administrations through combination. The quantity of IL-2 administered to mice to achieve the adjuvanting effect observed by Bubenik et al. would be different from the amount required for humans. The quantity required for sufficient administration is not a required element of the claims and even if it were, specific concentrations do not support patentable subject matter unless the concentration

is considered critical to the invention, see *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation for inducing a specific immune response with a composition comprising the IL-2 of Bubenik et al. with the papillomavirus proteins of Galloway because Bubenik et al. specifically teach augmenting the function of papillomavirus vaccines in cells expressing E6 and E7 and Galloway teaches therapeutic vaccines comprising E6 and E7. Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, absent unexpected results to the contrary.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shanon Foley whose telephone number is (571) 272-0898. The examiner can normally be reached on M-Th 6:00 AM - 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on (571) 272-0902. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Shanon Foley

SHANON FOLEY
PRIMARY EXAMINER